

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS : KONFINO et al.
APPLICATION SERIAL NO: 10/615,865
FILED : July 9, 2003
FOR : COPOLYMER-1 IMPROVEMENTS IN
COMPOSITIONS OF COPOLYMERS
EXAMINER : Examiner F. Krass
GROUP ART UNIT : 1614

Declaration of YAFIT STARK under 37 CFR §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Yafit Stark, Ph.D., currently residing at 22 Uziel Street, Givat Shmuel, Israel, hereby declare the following:

1. I am the Senior Director of the Global Clinical Research Corporate Innovative R & D Division at Teva Pharmaceuticals Ltd., the exclusive licensee of United States Patent Application No. 10/615,865, filed July 9, 2003, for which a patent is being sought in the present application. I have read and understood the present application, and I am highly familiar with Copaxone®, a preferred embodiment of the present invention, especially with respect to clinical studies involving this drug.
2. I received a Ph.D. degree from Tel Aviv University, Israel, in 1985. I have worked in the area of pharmaceutical research for Teva Pharmaceuticals since 1987. For the past 13 years, I have been personally responsible for the clinical development and research of Copaxone®. My *curriculum vitae* is attached.

3. I have been asked to comment on some of the purposes of the following clinical trials: "Clinical Trial Protocol No. 9001; first patient enrolled October 23, 1991" and "Clinical Trial Protocol No. 9002; first patient enrolled June 17, 1993," hereinafter referred to as "9001" and "9002", respectively.
4. One purpose of clinical trial 9001 was to verify that an improvement in a copolymer-1 composition, reducing toxicity by lowering the average molecular weight, did not diminish or negate the effectiveness of the composition in treating multiple sclerosis.
5. One purpose of clinical trial 9002 was to collect and verify the long-term safety of the improved copolymer-1 composition.
6. Thus, clinical trials 9001 and 9002 were necessary to verify the efficacy and pharmaceutical viability of the claimed invention.

I, Yafit Stark, declare under penalty of perjury that the above statements are true and correct to the best of our knowledge, information, and belief. I understand that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. 1001) and may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

Dated: 22/NOV/2004

Stark Yafit
Yafit Stark

CURRICULUM VITAE

Name: Yafit Stark Ph.D.

Title: Senior Director Global Clinical Research
Corporate Innovative R & D Division,
Teva Pharmaceuticals Ltd.

Home Address: 22 Uziel Street,
Givat Shmuel, Israel.

Tel (home): 03-5323343

Date & Place of Birth: 24 June, 1953, Israel.

Military Service (Zahal): 1971 - 1973

Marital Status: Married + 3 children

EDUCATION

1973 - 1976: B.Sc., Bar Ilan University, Physiology.
Zoology.

1976 - 1979: M.Sc., Tel Aviv University, Pathology.
Under the direction of Prof. M. Wolman.
"Study of the Combined Effect of Treatment with
Levan and Cytotoxic Drugs on the Development
and Cure of a Malignant Tumor in Mice".

1980 - 1985: Ph.D., Tel Aviv University, Pathology.
Under the direction of Prof. M. Wolman and
Dr. J. Leibovici. "The Direct Effect of Levan on
Tumor Cells: Conditions and Mechanisms".

1986 - 1987: Post-doctoral fellowship - Tel Aviv University and
the Weizman Institute, under the direction of
Prof. B. Grifell. "Epithelial Cell Differentiation -
Immuno-Histopathological Research".

POSITIONS HELD:

From Aug. 1994: Senior Director Global Clinical Research, Clinical Trials Department, Innovative R & D, TEVA Pharmaceutical Industries, Ltd., P. O. Box 8077, Kiryat Nordau, Netanya, Israel.

Responsible for;

- planning and execution of the clinical development plan of all the company's innovative drugs.
- Planning and execution of bioequivalence studies for the company's generic products.
- Providing clinical supplies for clinical studies, including packaging, distribution, follow-up, destruction and drug accountability for all global studies.
- Management of Drug Safety according to the relevant laws and regulations
- Ensuring compliance of clinical studies with ICH-GCP Guidelines, and in accordance with laws applicable in the relevant countries and Teva's Standard Operating Procedures.

1991-1994 Director of R&D Clinical Research, TEVA USA
Responsible for planning and execution of clinical trials in the USA for Teva's innovative drug, Copaxone

1990-1991 Clinical Studies Manager, Innovative R&D, TEVA Pharmaceutical Industries, Ltd. Israel
Responsible for managing clinical trials with TEVA's innovative compounds

1987-1990 Project Manager. Innovative R&D, TEVA Pharmacaetical Industries, Ltd., Israel
Responsible for development of products for the following indications: diabetes, hypertension, epilepsy, cancer, bone disease

COURSES TAKEN:

1. Good Clinical Practice in Clinical Trials
2. Design and Operation of Clinical Trials
3. Monitoring of Clinical Trials
4. International Clinical Studies Management
5. Cost Control, Operation and Strategy

6. Economic Outcomes and Quality of Life
7. Quality Control/Quality Assurance of Clinical Data
8. Safety Reporting in Clinical Trials
9. Pharmacovigilance
10. Statistics for Clinical Trials
11. Senior Managerial Course
12. Strategic Alliances Abroad
12. Business Management – Lahav Business School, Tel Aviv University
13. Companies acquisitions and mergers
14. Globalization in Industry
15. Course for Senior Directors in Corporations – Lahav Business School, Tel Aviv University

MEMBERSHIPS

Society for Clinical Trials, Inc.
600 Wyndhurst Avenue
Baltimore, Maryland 21210
U.S.A.

Drug Information Association
3113 Maple Glen, PA 19002
U.S.A.

American Society of Clinical Oncology (ASCO)
1900 Duke Street, Suite 200
Alexandria, VA 22314

American Society for Experimental NeuroTherapeutics (ASENT)
555 E. Wells Street, Suite 1100
Milwaukee, WI 53202-3823

International Society for Quality of Life Research (ISOQOL)
6728 Old McLean Village Drive
McLean, VA 22101-3906
USA

Association of Clinical Research Professionals (ACRP)
Global Headquarters (Washington, DC)
500 Montgomery Street, Suite 800
Alexandria, VA 22314
USA

List of Publications

1. Y. Stark, J. Leibovici and M. Wolman.
Effect of Administration Schedule on Levan the Cyclophosphamide
Combined Treatment of Lewis Lung Carcinoma.
Int. J. Immunopharmac. 5:289-297, 1983.
2. J. Leibovici, Y. Stark and M. Wolman.
Combined Effect of Levan and Cytotoxic Agents on the Growth of
Experimental Tumors in Mice.
Br. J. Exp. Path. 64:239-244, 1983.
3. J. Leibovici, S. Hoenig, Y. Stark, S. Kopel and M. Wolman.
Change from Inhibition to Stimulation by Levan of AKR Lymphomas
Following Serial Transfers.
Exp. Cell Biol. 52:219-244, 1984.
4. J. Leibovici and Y. Stark.
The Direct Antitumoral Effect of the Polysaccharide Levan: Effects of Drug
Concentration, Time and Temperature of Incubation.
J. Natl. Cancer Inst. 72:1417-1420, 1984.
5. M. Michowitz, Y. Stark and J. Leibovici.
Different Stages of Tumor Development are Unequally Affected by
Pretreatment of Tumor Cells with a Polysaccharide.
Cancer Lett., 23:343-349, 1984.
6. Y. Stark and J. Leibovici.
Effect of Levan on Tumorigenicity of Cells from Different Murine Tumors.
Cell. and Mol. Biol. 30:425-430, 1984.
7. J. Leibovici, Y. Stark and S. Kopel.
Different Biological Behavior of AKR Lymphoma Cells from Primary and
Metastatic Tumors.
Experientia, 41:404-407, 1985.
8. J. Leibovici and Y. Stark.
Increase in Cell Permeability to Cytotoxic Agents by the Polysaccharide
Levan.
Cell. Mol. Biol. 31:337-341, 1985.
9. Y. Stark and J. Leibovici.

Different Effects of the Polysaccharide Levan on Oncogenicity of Cells of Two Variants of Lewis Lung Carcinoma.
Br. J. Exp. Pathol. 67:141-147, 1986.

10. J. Leibovici and Y. Stark.
Slow Cytotoxicity of the Polysaccharide Levan on Tumor Cells In Vitro.
Chemico-Biol., Interact. 60:191-200, 1986.
11. Y. Stark and J.N. Whitaker.
Expanded Clinical Trials of Treatments for Multiple Sclerosis:
Copolymer-1 (COP-1) treatment investigational new drug (IND) program.
Ann. Neurol. 36:114-115, 1994.
12. K.P. Johnson, B.R. Brooks, J.A. Cohen, C.C. Ford et al, and the
Copolymer-1 Multiple Sclerosis Study Group.
Copolymer-1 reduces relapse rate and improves disability in relapsing-
remitting Multiple Sclerosis. Results of a phase III, multicenter, double-
blind, placebo-controlled trial.
Neurology, 45:1268-1276, 1995.
13. K.P. Johnson, B.R. Brooks, J.A. Cohen, C.C. Ford et al, and the
Copolymer-1 Multiple Sclerosis Study Group.
Extended use of Glatiramer acetate (Copaxone®) is well tolerated and
maintains its clinical effect on Multiple Sclerosis relapse rate and degree of
disability.
Neurology, 50: 701-706, 1998.

Submitted for Publication

1. J. Leibovici, Y. Stark, A. Jedeikin.
Combined Hyperthermia - Levan Treatment of Lewis Lung Carcinoma Cells.

Chapters in Books

1. J. Leibovici, Y. Stark, T. Eldar, G. Brudner, M. Wolman.
Mechanism of the Inhibitory Effect of Levan in Experimental Tumors. In:
Cancer Chemo- and Immunopharmacology 2.
Immunopharmacology, Relation and General Problems.
Recent Results in Cancer Research. Ed. G. Mathe and F.M. Mugia,
Springer-Verlag, Berlin, Heidelberg, New York, Vol. 75:173-179, 1980.

Papers presented at Scientific Meetings and Abstracts

1. Y. Stark, J. Leibovici, M. Michowitz and M. Wolman.
Variability of the Direct Effect of Levan on Tumor Cells.

- 13th FEBS Meeting, The Federation of European Biochemical Societies, Jerusalem, Israel, p. 186. 1980.
2. J. Leibovici, Y. Stark, S.. Hoenig and M. Wolman.
Mechanism of Direct Effect of Levan on Murine Tumore Cells.
14th FEBS Meeting, The Federation of European Biochemical Societies, Jerusalem, Israel, p.186, 1980.
 3. J. Leibovici, Y. Stark and m. Wolman.
Combined Effect of Levan and Cyclophosphamide on The Growth of Lewis Lung Carcinoma in C57BL Mice.
4th International Congress Immunology, Paris, 1980.
 4. J. Leibovici, Y. Stark and S. Kopel.
Differences in Biological Behavior of Primary and Metastatic AKR Lymphoma Cells.
The 1st Common Congress of Israelian Societies of Life Sciences, Jerusalem, Israel, 1983.
 5. J. Leibovici and Y. Stark.
Demonstration of Increased Permeability to a Fluorescent Cytotoxic Agent Induced by the Polysaccharide Levan.
The VIIth International Congress of Histochemistry and Cytochemistry, Helsinki, Finland, p. 244, 1984.
 6. J. Leibovici and Y. Stark.
Membranal Differences between AKR Lymphoma Cells of Different Malignant Potential.
The 16th Meeting of Federation of European Biochemical Societies (FEBS), Moscow, Soviet Union, p. 338, 1984.
 7. J. Leibovici and Y. Stark.
A Tumor Progress Model for Testing of Immunotherapeutic Agents. The 6th European Immunology Meeting, Interlaken, Switzerland, p. 174, 1984.
 8. Y. Stark and J. Leibovici.
Different Effects of the Polysaccharide Levan on Tumorigenicity in Various Murine Tumor Models.
Regional Scientific Meeting on Laboratory Animals and the Advancement of Science (ICLAS Meeting), Shores, Israel, p.34, 1985.
 9. J. Leibovici, Y. Stark, A. Jedeikin and G. Klorin.
Membranal Differences between Tumor Cells Sensitive or Resistant to a Polysaccharide Acting on Cell Membrane.
Clinical Chemistry and Enzymology. Meetings, Jerusalem, Israel, p.42, 1985
 - .10. G. Comi, M. Filippi and the Copaxone[®] MRI Study Group
The Effect of Glatiramer Acetate (Copaxone[®]) on Disease Activity as

measured by Cerebral MRI in Patients with Relapsing-Remitting Multiple Sclerosis.
ANA, 1998

11. G. Comi, M. Filippi and the Copaxone[®] MRI Study Group
The Effect of Glatiramer Acetate (Copaxone[®]) on Disease Activity as measured by Cerebral MRI in Patients with Relapsing-Remitting Multiple Sclerosis.
ANN 1999
12. J.S. Wolinsky, K.P. Johnson, G. Comi, A.E. Miller, D. Ladkani, G. Shifroni, Y. Stark & M. Filippi
Glatiramer Acetate Slows Sustained Accumulated Disability in Relapsing Multiple Sclerosis: Meta-Analysis Results of Three Double-Blind, Placebo-Controlled Clinical Trials
ANN 2003
13. P.K. Coyle, K. Johnson, L. Pardo and Y. Stark, on behalf of the Copaxone Research Team
Pregnancy Outcomes in Patients with Multiple Sclerosis treated with Glatiramer Acetate (Copaxone[®])
ANN 2003
14. J.S. Wolinsky, L. Pardo, Y. Stark, S. Silman, S. Kadosh, B. Zak, D. Ladkani and the PROMiSe Study Group
Effect of Glatiramer Acetate on Primary Progressive Multiple Sclerosis: Initial Analysis of the Completed PROMiSe Trial
ANN 2004